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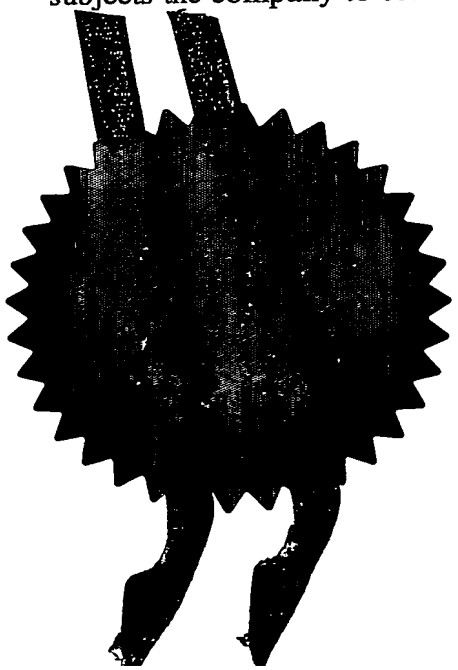

Signed Andrew Gerry

Dated 08 AUG 2004

Patents Form 1/77

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The Patent Office

Request for grant of a patent

(See the notes on the back of this form. You can also get an explanatory leaflet from the Patent Office to help you fill in this form)

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1.	Your reference	IB/G-32713P1/ABR 9929
2.	Patent application number *(The Patent Office will fill in this part)*	0325828.2
3.	Full name, address and postcode of the or of each applicant *(underline all surnames)*	SANDOZ GMBH BIOCHEMIESTRASSE 10 A-6250 KUNDL, TIROL AUSTRIA
	Patent ADP number *(if you know it)*	08638736001
	If the applicant is a corporate body, give the country/state of its incorporation	AUSTRIA
4.	Title of invention	Organic Compounds
5.	Name of your agent *(If you have one)*	Craig McLean
	"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*	Novartis Pharmaceuticals UK Limited Patents and Trademarks Wimblehurst Road Horsham West Sussex RH12 5AB
	Patents ADP number *(if you know it)*	07181522002

6.	If you are declaring priority from one ore more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number	Country	Priority application number *(if you know it)*	Date of filing (day/month/year)
7.	If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application		Number of earlier application	Date of filing (day/month/year)
8.	Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer 'Yes' if:* *a) any applicant named in part 3 is not an inventor, or* *b) there is an inventor who is not named as an applicant, or* *c) any named applicant is a corporate body.* *(see note (d))*	Yes		

Patents Form 1/77

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Continuation sheets of this form	
Description	29
Claim(s)	5
Abstract	1
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10. If you are also filing any of the following, state how many against each item.

Priority documents	
Translations of priority documents	
Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	
Request for preliminary examination and search *(Patents Form 9/77)*	1
Request for substantive examination *(Patents Form 10/77)*	
Any other documents *(please specify)*	

11. I/We request the grant of a patent on the basis of this application

Signature Date

Craig Mc Lean 4th November 2003

12. Name and daytime telephone number of person to contact in the United Kingdom

Mr. Trevor Drew 01403 323069

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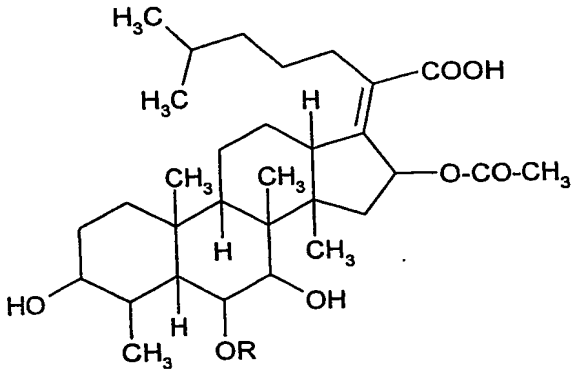
Organic Compounds

The present invention relates to organic compounds.

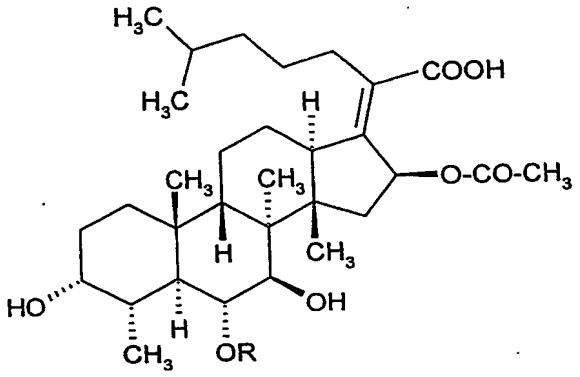
We have now surprisingly found organic compounds, e.g.a class of compounds having pharmacuetical, e.g. antibacterial, activity.

In one aspect the present invention provides a compound of formula



I

e.g. including a compound of formula



I_P

wherein

R is hydrogen, CO-R_1 or (C_{1-8})alkyl, such as methyl, ethyl, n-propyl or n-hexyl, and

R_1 is hydrogen, (C_{1-8})alkyl, such as ethyl, n-propyl, isopropyl, 2-ethylpropyl, 1,1-dimethylpropyl, n-butyl, isobutyl, t.butyl, n-pentyl, t.butylmethyl, n-hexyl; (C_{3-8})cycloalkyl, (C_{1-8})alkoxy-(C_{1-6})alkyl, (C_{1-4})alkoxy-(C_{1-4})alkoxy-(C_{1-4})alkyl, amino(C_{1-4})alkyl, halo(C_{1-6})alkyl, hydroxy(C_{1-4})alkyl, carboxy(C_{1-4})alkyl, (C_{1-4})alkoxycarbonyl-(C_{1-4})alkyl, (C_{6-18})aryl, heterocyclyl having 5 or 6 ring members and 1 to 4 heteroatoms selected from S, O or N, or brigded (C_{7-12})cycloalkyl;

e.g. wherein

- cycloalkyl is unsubstituted or substituted, such as unsubstituted cycloalkyl or cycloalkyl one or more fold substituted by (C_{1-4})alkyl or (C_{1-4})alkoxy, such as 1-methyl-cycloprop-1-yl, 2-methyl-cyclopropyl, 2,2,3,3-tetramethyl-cyclopropyl, 3-methoxy-cyclohexyl, 4-methoxy-cyclohexyl;
- amino is unsubstituted or substituted, e.g. unsubstituted or substituted by (C_{1-4})alkyl, di(C_{1-4})alkyl, or (C_{1-4})alkoxycarbonyl; e.g. (C_{1-4})alkoxycarbonyl, such as methoxycarbonyl,
- aryl is unsubstituted or substituted by amino.

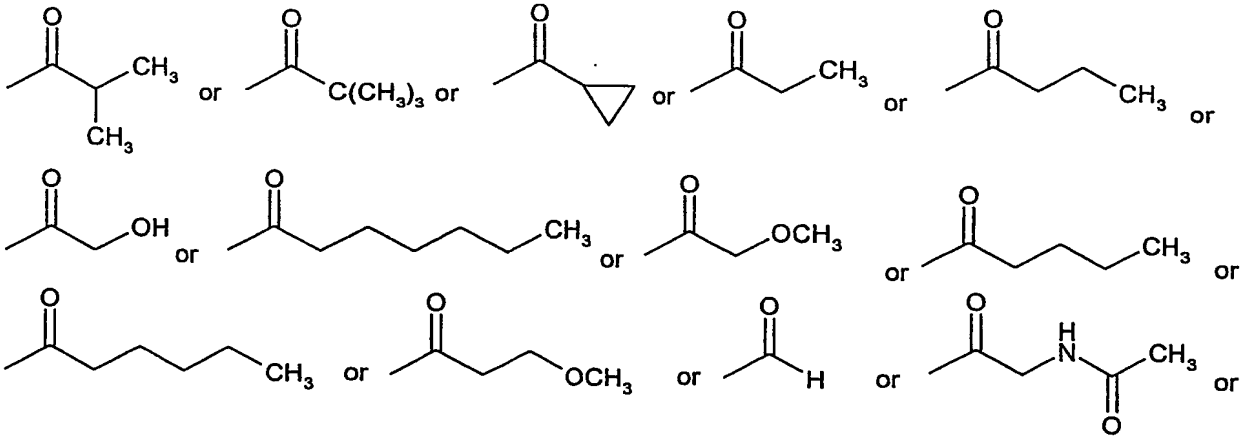
Preferably in a compound of formula I

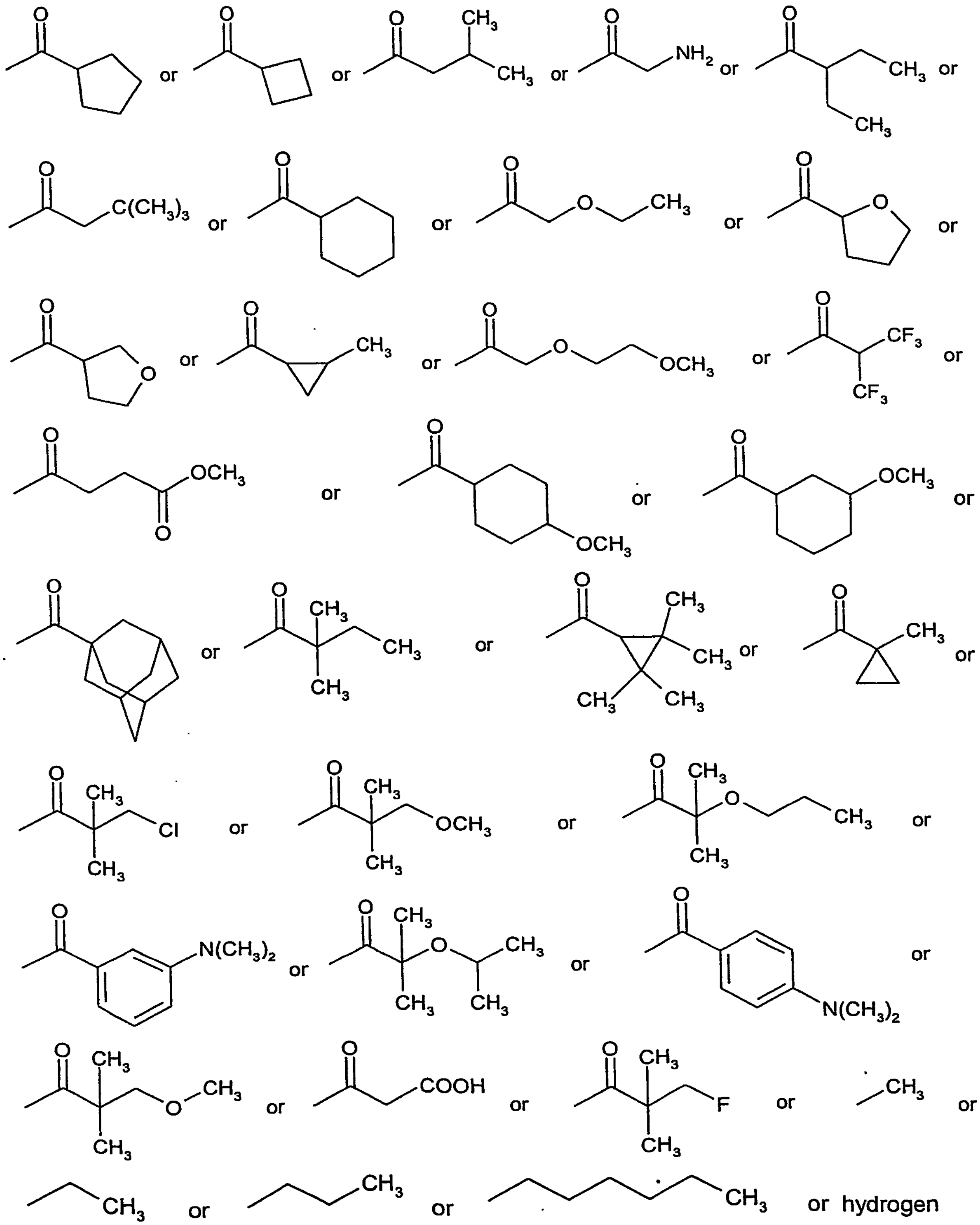
-R is hydrogen, (C_{1-6})alkyl, or CO-R_1,

- R_1 is hydrogen, (C_{1-6})alkyl, (C_{3-6})cycloalkyl, e.g. unsubstituted (C_{3-6})cycloalkyl or (C_{3-6})cycloalkyl substituted by one or more methyl or methoxy; (C_{1-3})alkoxy-(C_{1-3})alkyl, methoxy-(C_{1-2})alkoxy-(C_{1-2})alkyl, aminomethyl, e.g. including methoxycarbonylamino; halo(C_{1-4})alkyl comprising one or two halogen atoms; hydroxymethyl, carboxymethyl, methoxycarbonyl-(C_{1-2})alkyl, phenyl, e.g. phenyl substituted by amino, such as dimethylamino; tetrahydrofuranyl or adamantanyl.

In a compound of formula I or I_P, respectively, each single defined substitutent may be a preferred substituent, e.g. independently of each other substitutent defined.

In another aspect the present invention provides a compound of formula I, wherein R is a group of formula





or hydrogen

If not otherwise defined herein

- alkyl includes (C_{1-8})alkyl, such as (C_{1-6})alkyl, e.g. (C_{1-4})alkyl;
- cycloalkyl includes (C_{3-8})cycloalkyl, e.g. (C_{3-6})cycloalkyl, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl:
- alkoxyalkyl includes (C_{1-6})alkoxy-(C_{1-6})alkyl, such as (C_{1-4})alkoxy-(C_{1-4})alkyl, e.g. methoxymethyl, ethoxymethyl, 1,1-dimethyl-1-n-propoxymethyl, 1,1-dimethyl-1-isopropoxymethyl, methoxyethyl, 1,1-dimethyl-1-methoxy-methyl;
- alkoxy includes (C_{1-6})alkoxy, such as (C_{1-3})alkoxy; e.g. methoxy, ethoxy, propoxy;
- haloalkyl includes halo(C_{1-6})alkyl, e.g. halo(C_{1-4})alkyl, comprising one or more halogen atoms, e.g. including (C_{1-4})alkyl substituted by one or more CF_3, such as -$CH(CF_3)_2$, 1,1-dimethyl-2-fluoroethyl, or 1,1-dimethyl-2-chloroethyl;
- hydroxyalkyl includes hydroxy(C_{1-4})alkyl, such as hydroxymethyl;
- carboxyalkyl includes carboxy(C_{1-4})alkyl, such as carboxymethyl;
- alkoxycarbonylalkyl includes (C_{1-4})alkoxycarbonyl-(C_{1-4})alkyl, such as methoxycarbonyl-(C_{1-4})alkyl, e.g. methoxycarbonylethyl;
- alkoxy-alkoxy-alkyl includes (C_{1-4})alkoxyl-(C_{1-4})alkoxy-(C_{1-4})alkyl, e.g. methoxy-ethoxy-ethyl;
- aminoalkyl includes amino(C_{1-4})alkyl, such as aminomethyl;
- amino includes unsubstituted amino and amino substituted by (C_{1-4})alkyl, di(C_{1-4})alkyl, or (C_{1-4})alkoxycarbonyl; such as dimethylamino, methoxycarbonylamino;
- heterocyclyl includes heterocyclyl having 5 or 6 ring members and 1 to 4 heteroatoms selected from S, O and N, e.g. heterocyclyl having 5 ring members, e.g. the heteroatom is selected from O, such as tetrahydrofurane;
- aryl includes (C_{6-18})aryl, such as phenyl;
- brigded cycloalkyl includes cycloalkyl bridged by alkyl, e.g. bridged (C_{7-12})cycloalkyl, such as bridged (C_{10})cycloalkyl, e.g. adamantanyl;
- halogen includes fluoro, chloro, bromo, iodo, e.g. fluoro, chloro.

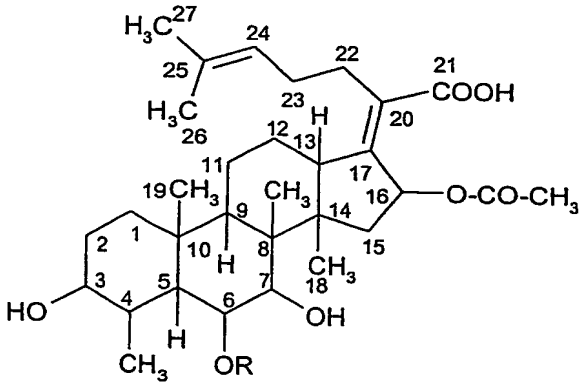
Compounds provided by the present invention are hereinafter designated as "compound(s) of (according to) the present invention". A compound of formula I includes a compound of formula I_P. A compound of the present invention includes a compound in any form, e.g. in free form, in the form of a salt, in the form of a solvate and in the form of a salt and a solvate.

In another aspect the present invention provides a compound of the present invention in the form of a salt.

Such salts include preferably pharmaceutically acceptable salts, although pharmaceutically unacceptable salts are included, e.g. for preparation / isolation / purification purposes.
A salt of a compound of the present invention includes a metal salt or an acid addition salt. Metal salts include for example alkali or earth alkali salts, e.g. a sodium salt. Acid addition salts include salts of a compound of formula I with an acid, e.g. hydrogen fumaric acid, fumaric acid, naphthalin-1,5-sulphonic acid, hydrochloric acid, deuterochloric acid.
A compound of the present invention in free form may be converted into a corresponding compound in the form of a salt; and vice versa. A compound of the present invention in free form or in the form of a salt and in the form of a solvate may be converted into a corresponding compound in free form or in the form of a salt in non-solvated form; and vice versa.

A compound of of the present invention may exist in the form of isomers and mixtures thereof; e.g. optical isomers, diastereoisomers, cis/trans conformers. A compound of the present invention may e.g. contain asymmetric carbon atoms and may thus exist in the form of enatiomers or diastereoisomers and mixtures thereof, e.g. racemates. Substituents at any asymmetric carbon atom may be present in the (R)-, (S)- or (R,S)-configuration, preferably in the (R)- or (S)-configuration. E.g., a compound of formula I has several asymmetric C-atoms and substitutents bound to such asymmetric C-atoms may be in the (R)- and in the (S)-configuration, e.g. including mixtures thereof, e.g. as set out in a compound of formula I_P. Preferably a compound of formula I is a compound of formula I_P. Also a compound of formula I has a double bond and substituents bound to that double bond may be in the form of cis- or trans conformers, or mixtures thereof.
Isomeric mixtures may be separated as appropriate, e.g. according, e.g. analogously, to a method as conventional, to obtain pure isomers. The present invention includes a compound of the present invention in any isomeric form and in any isomeric mixture.
The present invention also includes tautomers of a compound of formula I, where tautomers can exist.

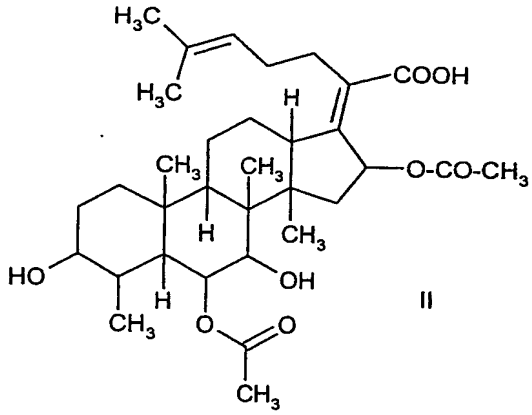
In the following it is referred to the numbering system of the ring structure and substituents as set out in a compound of formula I below:



I NUMBER

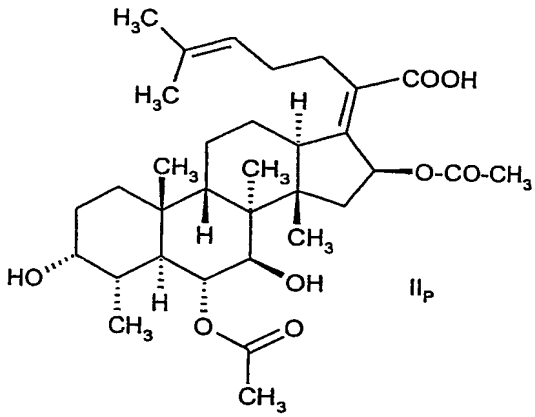
In another aspect the present invention provides a process for the production of a compound of formula I comprising the steps

a. protecting the carboxy group of position 21 and optionally the hydroxy group attached to the ring structure in position 3 of the ring structure in a compound of formula



II

such as of formula



II_P

to obtain a compound of formula II, or II_P, respectively, wherein the carboxy group of position 21 is protected and the hydroxy group attached to the ring structure in position 3 is optionally protected,

b. splitting off the acetyl group from the acetoxy group in position 6 of the ring structure from a compound as obtained in step a., to obtain a compound as obtained in step a, wherein the group attached to position 6 of the ring structure is hydroxy,

c1. either hydrogenating the double bond in positions 24 and 25 and, e.g. in the course of double bond hydrogenation, splitting off the protecting group(s) from a compound as obtained in step b., to obtain a compound of formula I, wherein R is H, or

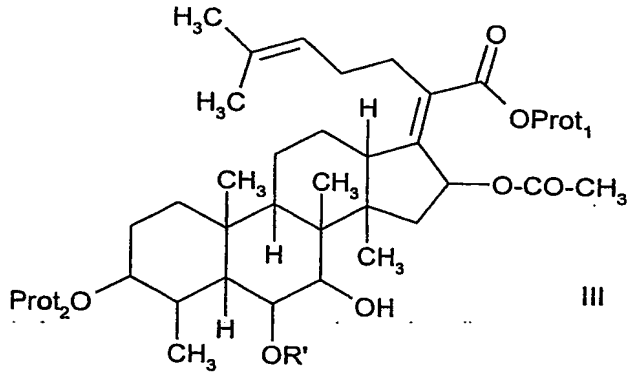
c2. reacting a compound as obtained in step b. with a (C_{1-8})alkylhalogenide, hydrogenating the double bond in positions 24 and 25, and, e.g. in the course of double bond hydrogenation, splitting off the protecting group(s), to obtain a compound of formula I, wherein R is (C_{1-8})alkyl, or

c3. reacting a compound as obtained in step a. with a compound of formula R'_1-COOH, wherein R'_1 has the meaning of R_1 as defined above, and additionally includes residues as defined in R_1, wherein functional groups, such as amino, hydroxy, carboxyl, are protected, either in the presence of a condensation agent, or with a compound of formula R'_1-COOH, wherein R'_1 is as defined above, in a reactive form, e.g. in the form of a carboxylic acid halogonide, to obtain a compound as obtained in step b., wherein the group attached to the ring structure in position 6 is a group of formula CO-R'_1, wherein R'_1 is as defined above, hydrogenating the double bond in positions 24 and 25, and, e.g. in the course of double bond hydrogenation, splitting off the protecting group(s), to obtain a compound of formula I, wherein R is a group of formula CO-R_1, wherein R_1 is as defined above, or wherein R is a group of formula CO-R'_1, wherein R'_1 is as defined above, and optionally splitting of protecting groups in R'_1, e.g. if (still) present, and

d. isolating a compound of formula I as obtained in step c. from the reaction mixture.

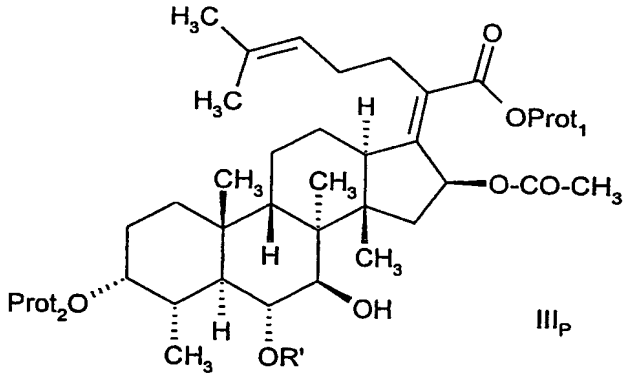
The protecting group attached to the carboxy group of position 21 is present, and the protecting group attached at oxygen atom attached to the ring structure in position 3, is optionally present. The reaction works in both cases, but, e.g. to obtain higher purity of the reaction products, both protecting groups are preferably present. Protecting groups include groups as appropriate, e.g. such as conventional, preferably protection groups which may be splitt off by hydrogenation under conditions, under which the double bond in positions 24 and 25 is converted into a single bond. Such groups e.g. include benzyloxymethyl and diphenylmethyl groups, e.g. and benzyl groups. E.g.the protection group attached to the group of position 21 is benzoxymethyl, and the protecting group attached to the oxygen atom which oxygen atom is attached to the ring structure in position 3, is either other than a protecting group, e.g. hydrogen, or benzoxymethyl, or diphenylmethyl.
R'_1 has the meaning of R_1 as defined above and additionally includes residues as defined in R_1, wherein functional groups, such as hydroxy, carboxyl and amino, are protected, e.g. hydroxy or carboxyl are protected by a benzyl group; amino is protected by a benzyloxycarbony groupl; e.g. residues of R_1 having functional groups such as amino, carboxy or hydroxy, are in a protected form, e.g. in the form of benzyloxycarbonylamino, benzyloxy or benzyloxycarbonyl. Such protecting groups may be splitt off in the course of double bond hydrogenation in position 24 and 25, or at an appropriate stage.

In another aspect the present invention provides a process for the production of a compound of formula I, wherein R is as defined above, comprising hydrogenating the double bond in positions 24 and 25 and splitting off the protecting group(s), e.g. in the course of double bond hydrogenation, in a compound of formula



III

such as of formula



III_P

wherein

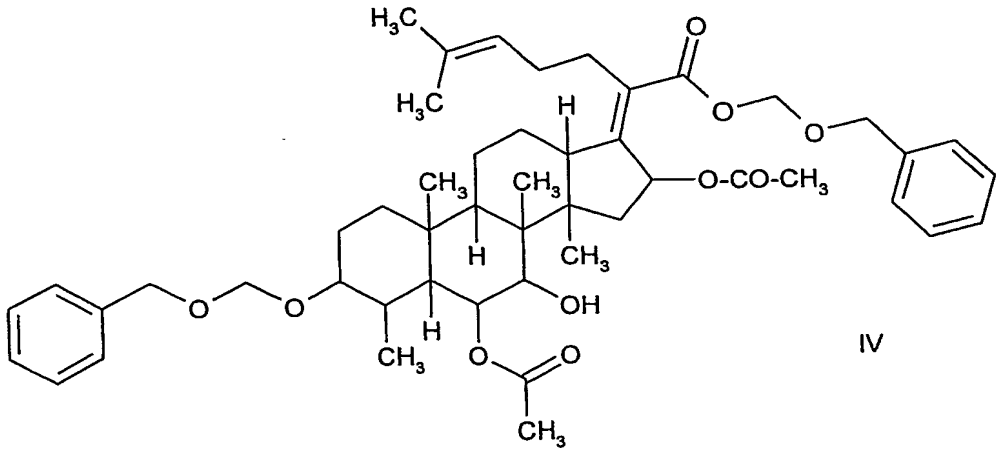
$Prot_1$ is a protecting group, such as benzyloxymethyl or diphenylmethyl, e.g. benzyloxymethyl,

$Prot_2$ is either other than a protecting group, or is a protecting group, e.g. $Prot_2$ is H, benzyloxymethyl or diphenylmethyl, and R' has the meaning of R as defined above and additionally includes residues as defined in R, wherein functional groups, such as amino, hydroxy, carboxyl groups, are protected.

In a preferred embodiment, a compound of formula I may be produced by a process comprising the steps

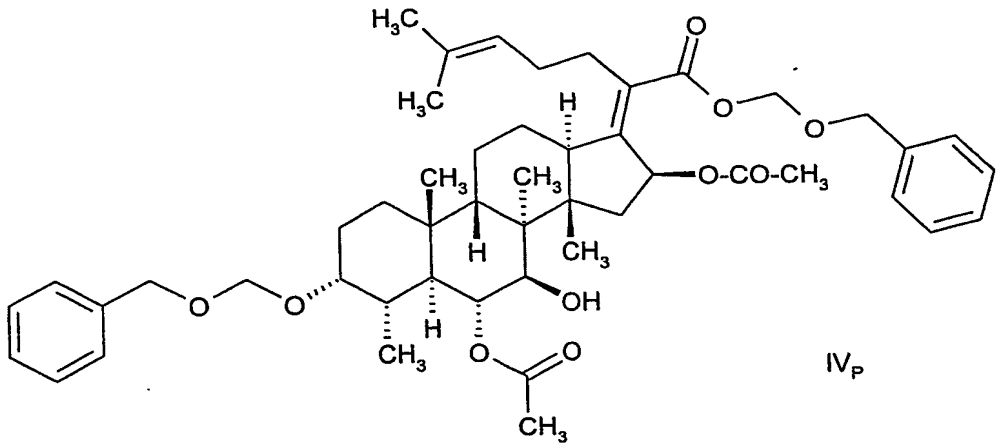
a. reacting a compound of formula II, or II_P, respectively,
with benzyloxymethylchloride in the presence of a base, e.g. Hünig`s base, in organic solvent, e.g. an halogenated hydrocarbon, such as CH_2Cl_2,

to obtain a compound of formula



IV

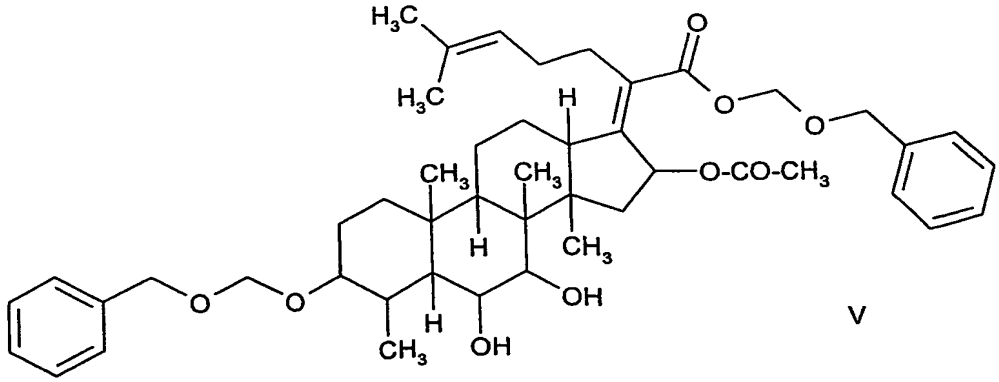
such as of formula



IV_P

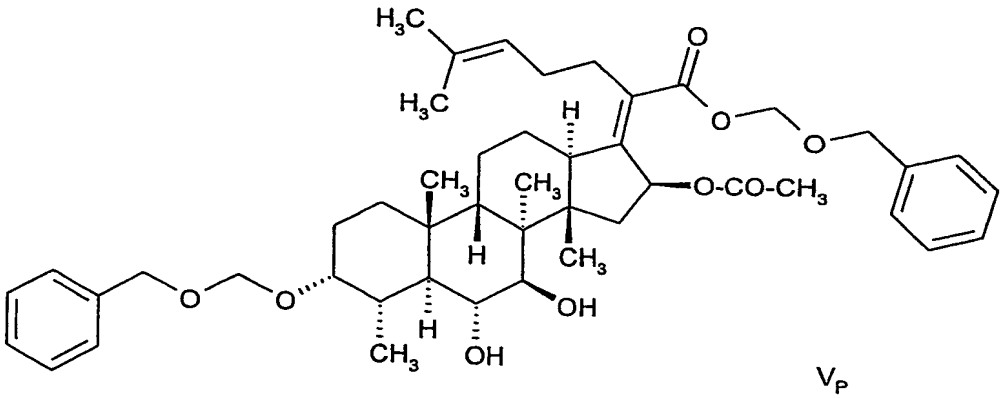
b. reacting a compound of formula IV, or IV_P, respectively, with a base, e.g. an alkali or earth alkali hydroxide, such as NaOH, in organic solvent, e.g. aqueous organic solvent, e.g. in a solvent mixture, such as terahydrofuran/MeOH/H_2O,

to obtain a compound of formula



V

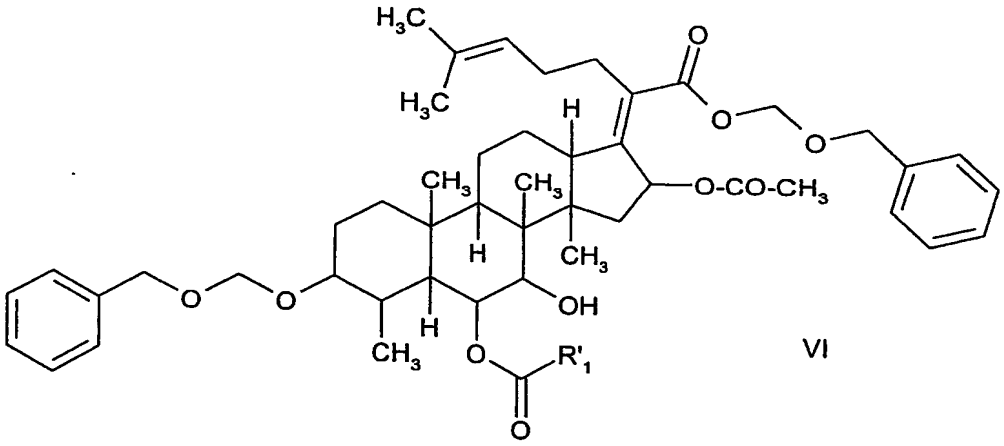
such as of formula



V_P

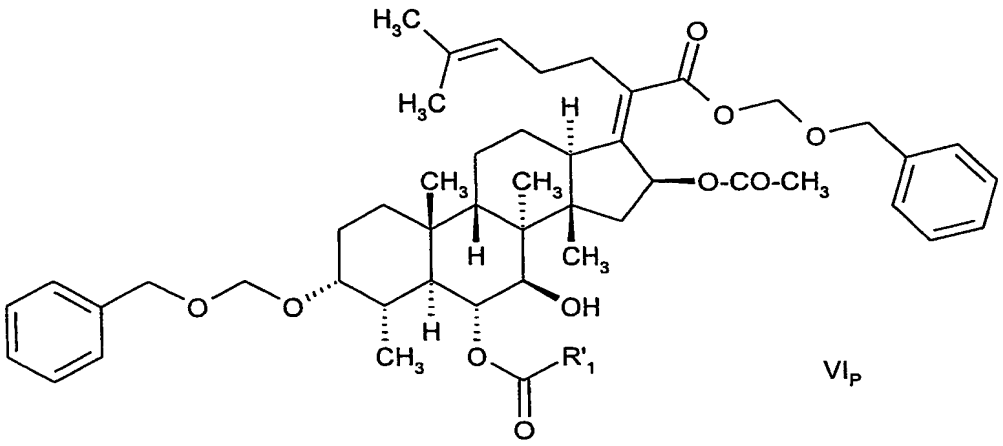
c1. reacting a compound of formula V, or V_P, respectively, with a compound of formula R'_1-COOH, wherein R'_1 has the meaning of R_1 as defined above and additionally includes residues as defined in R_1, wherein functional groups, such as amino, hydroxy, carboxyl, groups are protected, in the presence of a condensation agent, such as N`-(3-dimethylamino-propyl)-N-ethylcarbodiimide hydrochloride, and in the presence of a base, e.g. 4-dimethylaminopyridine, in organic solvent, e.g. halogenated hydrocarbon, such as CH_2Cl_2, or

c2. reacting a compound of V, or V_P, respectively, with a compound of formula R'_1-COCl, wherein R'_1 has the meaning of R_1 as defined above, and additionally includes residues as defined in R_1, wherein functional groups, such as amino, hydroxy, carboxyl groups, are protected, in the presence of a base, such as pyridine and 4-dimethylaminopyridine, to obtain a compound of formula



VI

such as of formula



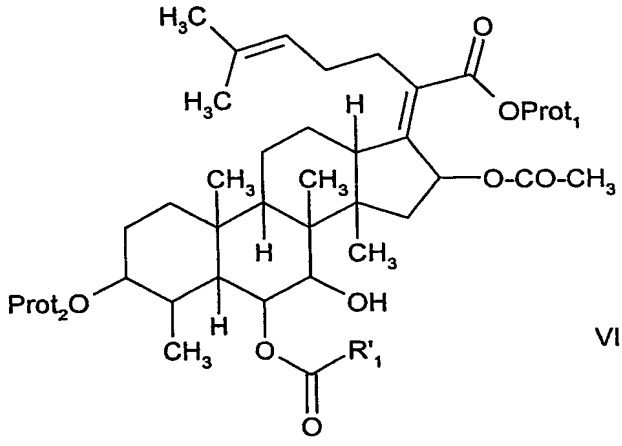
VI_P

wherein R'_1 is as defined above,

d. hydrogenating the double bond in positions 24 and 25 in a compound of formula VI, or VI_P, respectively, e.g. by reaction with H_2, in the presence of a catalyst, such as palladium, e.g. $Pd(OH)_2/C$, and, e.g. in the course of double bond hydrogenation splitting off protecting group(s), and optionally splitting off protection groups in R'_1, and

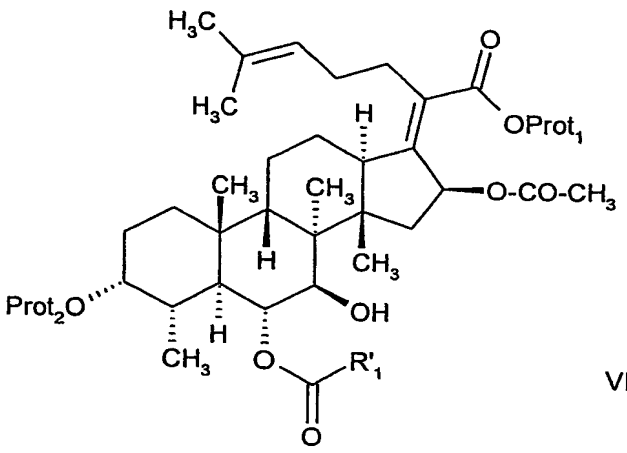
e. isolating a compound of formula I, or I_P, respectively, wherein R is $-COR_1$, and R_1 is as defined above as obtained in step d. from the reaction mixture.

In another aspect the present invention provides a compound of formula



VII

such as of formula



VII_P

wherein

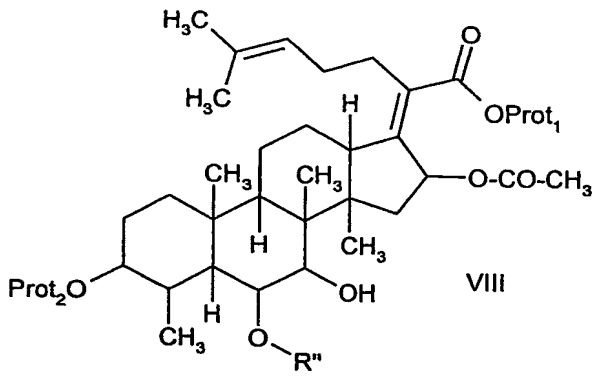
$Prot_1$ is a protecting group, such as benzyloxymethyl or diphenylmethyl, e.g. benzyloxymethyl, and

$Prot_2$ is either other than a protecting group, or is a protecting group, e.g. $Prot_2$ is H, benzyloxymethyl or diphenylmethyl, and R'_1 is as defined above, e.g. which compounds of formula VII, or VII_P, respectively, are useful as intermediates in the production of a compound of formula I, or I_P, respectively.

A compound of formula VII, or VII_P, respectively, includes compounds of formulae VI, or VI_P, respectively.

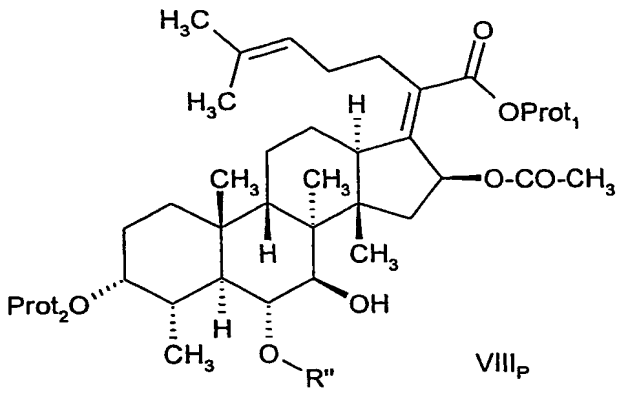
In another aspect the present invention provides a compound of formula IV, or IV_P, respectively, and of formula V, or V_P, respectively and of formula VI, or VI_P, respectively, wherein R'_1 is as defined above, which compounds are useful as intermediates in the production of a compound of formula I, or I_P, respectively, wherein R is a group $-CO-R_1$.

In another aspect the present invention provides a compound of formula



VIII

such as of formula



$VIII_P$

wherein $Prot_1$ and $Prot_2$ are as defined above, and R" is (C_{1-8})alkyl;
e.g., which compounds are useful as intermediates in the production of a compound of formula I, or I_P, respectively, wherein R is (C_{1-8})alkyl.

In a compound of formula VIII, or $VIII_P$, respectively, **preferably**

- $Prot_1$ is diphenylmethyl,
- $Prot_2$ is benzyloxymethyl
- R" is (C_{1-6})alkyl, e.g. methyl, ethyl, n-propyl or hexyl.

A compound of the present invention of formulae II, II_P, III, III_P, IV, IV_P, V, V_P, VI, VI_P, VII, VII_P, VIII and $VIII_P$ is herein also designated as "an intermediate of (according to) the present invention". An intermediate of the present invention includes an intermediate in any form, e.g. in free form, in the form of a salt, in the form of a solvate and in the form of a salt and a solvate.

In another aspect the present invention provides an intermediate of the present invention in the form of a salt.

Such salts include pharmaceutically acceptable salts and pharmaceutically unacceptable salts, e.g. for preparation / isolation / purification purposes. A salt of an intermediate of the present invention includes a metal salt or an acid addition salt. Metal salts include for example alkali or earth alkali salts, e.g. a sodium salt. Acid addition salts include salts of a compound of formula I with an acid, e.g. hydrogen fumaric acid, fumaric acid, naphthalin-1,5-sulphonic acid, hydrochloric acid, deuterochloric acid.

An intermediate of the present invention may exist in the form of isomers and mixtures thereof; e.g. optical isomers, diastereoisomers, cis/trans conformers, similarly as described above for a compound of the present invention.Isomeric mixtures may be separated as appropriate, e.g. according, e.g. analogously, to a method as conventional, to obtain pure isomers. The present invention includes an intermediate of the present invention in any isomeric form and in any isomeric mixture.
The present invention also includes tautomers of an intermediate of the present invention, where tautomers can exist.

In an intermediate of the present invention beside the (Prot-) protected groups, further functional groups, where present, optionally may be in protected form, e.g. amino, hydroxy or carboxyl groups, as indicated above; or may be in the form of a salt, where a salt-forming group is present. Protecting groups, optionally present beside $Prot_1$ and $Prot_2$, may be removed at an appropriate stage, e.g. according, e.g. analogously, to a method as conventional.

A compound of formula I, or I_P, respectively, obtained by a process provided by the present invention may be converted into another compound of formula I, or I_P, respectively, e.g. or a compound of formula I, or I_P, respectively, obtained in free form may be converted into a salt of a compound of formula I, or I_P, respectively, and vice versa.

Any compound described herein, e.g. a compound of the present invention and intermediates of formula II, II_P, III, III_P, IV, IV_P, V, V_P, VI, VI_P, VII, VII_P, VIII and $VIII_P$ may be prepared as appropriate, e.g. according, e.g. analogously, to a method as conventional, e.g. or as specified herein.

The compounds of the present invention, e.g. including a compound of formula I and of formula I_P, exhibit pharmacological activity and are therefore useful as pharmaceuticals.
The compounds of the present invention, e.g. including a compound of formula I and of formula I_P, exhibit pharmacological activity and are therefore useful as pharmaceuticals.
E.g., the compounds of the present invention show antimicrobial, e.g. antibacterial activity against gram positive bacteria and gram negative, such as Staphylococcus, e.g. S. aureus, MRSA (Methicillin Resistant S. aureus), MSSA (Methicillin Sensitive S. aureus), Enterococcus, e.g. E. faecalis, E.faecium, Moraxella, e.g. M.catarrhalis,

in vitro in the Agar Dilution Test and/or Micro Dilution Test for bacteria according to National Committee for Clinical Laboratory Standards (NCCLS) 1993,

- Document M7-A4, Vol. 20, No.2, 2000: "Methods for dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically" - Third Edition, Approved Standard"; and
- Document M26-A, Vo. 19, No. 18, 1999: Methods for determining antibactericidal activity of antimicrobial agents,
- Document M11-A3 for anaerobic bacteria,

in a concentration from about 0.1 to ca. 25.6 µg/ml, e.g. using strains including Staphylococcus aureus (ATCC 29213 and ATCC 29506); Enterococcus faecalis ATCC 29212;

and in vivo in the septicaemia mouse model, in accordance to the method description Nr. 159 A-5, approved by Austrian Health Authorities (MA 58, no. 2968/95 of 12-Oct-1995), e.g. when administered at dosages from 0.05 to 50 mg/kg body weight.

E.g., mice infected with Staphylococcus aureus (ATCC 49951, MSSA), and treated orally 1 and 4 hours after infection with a compound of example 1, e.g. in the form of its sodium salt, show an ED_{50} value of ca. 8.52 mg/kg body weight (ranging from 3.92 to 12.72). . Mice infected with S. aureus B29 (clinical isolate, MRSA) and treated orally 1 and 4 hours after infection with a compound of example 1, e.g. in the form of its sodium salt, show an ED_{50} value of ca. 4.66 mg/kg body weight, (ranging from 1.58 to 7.80). The ED_{50} values are calculated by Probit analysis of the administered dosages of compounds. Activity is determined by numbers of surviving animals per group of 8 or 6 mice, respectively, per dosage unit on day 5 after infection.

The compounds of the invention show a surprising overall activity spectrum.

It has, for example, been determined that the MIC (µg/ml) of the compound of Example 1, e.g. in the form of its sodium salt, against, for example Moraxella catarrhalis is of ca. 0.1 to 0.5; against Staphylococcus aureus is of ca. 0.2 to 12.5, and of Enterococcus faecalis is of ca. 6.4.

The compounds of the present invention are therefore useful for the treatment of microbial, e.g. bacterial diseases, e.g. the treatment of diseases associated with bacterial infections. Treatment includes treatment and prevention (prophylaxis).

In another aspect the present invention provides a compound of the present invention for use as a pharmaceutical, e.g. in the treatment of diseases associated with microbial, such as

bacterial infections.

In another aspect the present invention provides the use of a compound of the present invention for the manufacture of a medicament, e.g. in the form of a pharmaceutical composition, for the treatment of a microbial disease, such as bacterial diseases, for example of diseases associated with bacterias such as Staphylococcus spp. and Moraxella catarrhalis.

The compound of example 1 is a preferred compound of the present invention.
It has, for example been determined that the minimum inhibitory concentration, e.g. MIC90 (µg/ml), of the compound of Example 1, e.g. in the form of its sodium salt, against, for example S. aureus (MRSA) is of about 0.4. It is therefore, indicated that for the treatment of bacterial diseases, the compounds of the present invention may be administered to larger mammals, for example humans, by similar modes of administration at similar dosages than conventionally used with Linezolid.

In a further aspect the present invention provides a method of treatment of microbial, e.g. bacterial, diseases, e.g. diseases mediated by bacterias such as Staphylococcus spp. and Moraxella, which treatment comprises administering to a subject in need of such treatment an effective amount of a compound of the present invention; e.g. in the form of a pharmaceutical composition, e.g. in combination with another pharmaceutically active agent.

For pharmaceutical use a compound of the present invention includes one or more, preferably one, compounds of the present invention, e.g. a combination of two or more compounds of the present invention.
For such treatment, the appropriate dosage will, of course, vary depending upon, for example, the chemical nature and the pharmakokinetic data of a compound of the present invention employed, the individual host, the mode of administration and the nature and severity of the conditions being treated. However, in general, for satisfactory results in larger mammals, for example humans, an indicated daily dosage is in the range from about 0.01g to about 1.0 g of a compound of the present invention; conveniently administered, for example, in divided doses up to four times a day.

A compound of the present invention may be administered by any conventional route, for

example enterally, e.g. including nasal, buccal, rectal, oral, administration; parenterally, e.g. including intravenous, intramuscular, subcutanous administration; or topically; e.g. including epicutaneous, intranasal, intratracheal administration;
e.g. in form of coated or uncoated tablets, capsules, (injectable) solutions, solid solutions, suspensions, dispersions, solid dispersions; e.g. in the form of ampoules, vials, in the form of creams, gels, pastes, inhaler powder, foams, tinctures, lip sticks, drops, sprays, or in the form of suppositories.
The compounds of the present invention may be administered in the form of a pharmaceutically acceptable salt, e.g. an acid addition salt or metal salt; or in free form; optionally in the form of a solvate. The compounds of the present invention in the form of a salt exhibit the same order of activity as the compounds of the present invention in free form; optionally in the form of a solvate.

A compound of the present invention may be used for pharmaceutical treatment according to the present invention alone, or in combination with one or more other pharmaceutically active agents. Such other pharmaceutically active agents include other antibactials, e.g. penicillins, cephalosporins, macrolides. Combinations include fixed combinations, in which two or more pharmaceutically active agents are in the same formulation; kits, in which two or more pharmaceutically active agents in separate formulations are sold in the same package, e.g. with instruction for co-administration; and free combinations in which the pharmaceutically active agents are packaged separately, but instruction for simultaneous or sequential administration are given.

In another aspect the present invention provides a pharmaceutical composition comprising a compound of the present invention in association with at least one pharmaceutical excipient, e.g. appropriate carrier and/or diluent, e.g. including fillers, binders, disintegrators, flow conditioners, lubricants, sugars and sweeteners, fragrances, preservatives, stabilizers, wetting agents and/or emulsifiers, solubilizers, salts for regulating osmotic pressure and/or buffers,
e.g and further comprising another pharmaceutically active agent.

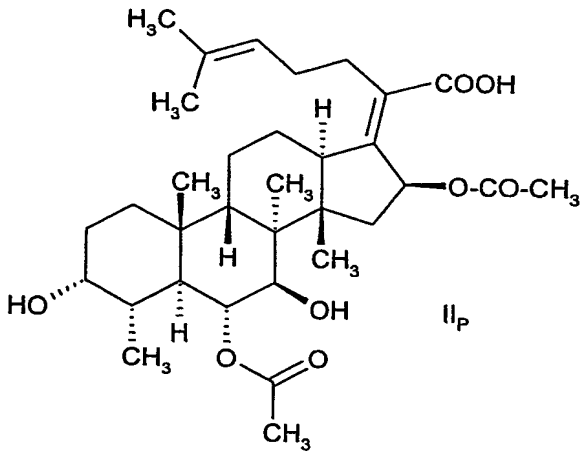
Such compositions may be manufactured according, e.g. analogously, to a method as conventional, e.g. by mixing, granulating, coating, dissolving or lyophilizing processes. Unit

dosage forms may contain, for example, from about 0.5 mg to about 1000 mg, such as 1 mg to about 500 mg.

In the following Examples all temperatures are in degrees Celsius (°C) and are uncorrected. The following abbreviations are used:

Bn	benzyl	BOM	benzyloxymethyl
Cbz	benzyloxycarbonyl	DMAA	N,N-dimethylacetamide
DMAP	4-dimetylaminopyridine	LiHMDS	Lithium bis(trimethylsilyl)amide
EDCI	N'-(3-dimethylaminopropyl)-N-ethylcarbodiimide in the form of a hydrochloride		
EtOAc	ethyl acetate	EX	Example
PE	petrolether	PPTS	pyridinium p-toluenesulfonat
rt	room temperature	THF	tetrahydrofurane
DPM	Diphenylmethyl		

Cephalosporin P1 is a compound of formula II_P.



II_P

EXAMPLE 1

6-O-isobutyryl-24, 25-dihydro-Cephalosporin P1 (compound of formula I, wherein R is -COR_1, wherein R_1 is isopropyl):

A. 3-O-Benzyloxymethyl-cephalosporin P1-benzyloxymethylester (compound of formula IV_P)

9.68 ml of BOM-Cl are added to a solution of 10 g of Cephalosporin P1 and 12.2 ml of Hünig's base in 40 ml of anhydrous CH_2Cl_2 at -10 °C. The reaction mixture obtained is stirred for 15 minutes and allowed to warm up to rt, and stirring is continued under argon for 24 hours. H_2O is added to the mixture obtained, two phases are obtained and are separated. The organic layer obtained is washed with H_2O, brine and saturated aqueous Na_2CO_3-solution, dried and solvent is evaporated. 3-O-Benzyloxymethyl-Cephalosporin P1 benzyloxymethylester is obtained.

^{1}H-NMR (200MHz, DMSO+D_2O): δ (ppm) = 7.32-7.37 (m, 10H, arom.-H), 5.66 (d, J=8.5Hz, H-16), 5.32 (dd, J=6.2Hz, J=16.3Hz, 2H, BOM-CH_2), 5.08 (t, J=6.4Hz, 1H, 24-H), 4.57-4.83 (m,7H,6-H,3x BOM-CH_2),3.54(s, 1H, 3-H),3.34(s,1H,7-H),2.00/1.84 (2s, 2 x 3H, H-34, H-36).

B. 3-O-Benzyloxymethyl-6-deacetyl-Cephalosporin P1 benzyloxymethylester (compound of formula V_P)

6.97 ml of 2N NaOH are added at 0°C to a solution of 11.38 g of 3-O-benzyloxymethyl-Cephalosporin P1 benzyloxymethylester in 75 ml of a mixture of THF/MeOH/H_2O = 5/4/1. To the reaction mixture obtained 20 ml of THF are added, in order to obtain a clear solution which is stirred at rt for 16 hours. 1.4 ml of 2N NaOH are added to the mixture obtained, solvent from the mixture obtained is evaporated, the residue obtained is distributed between H_2O and Et_2O, the mixture obtained is extracted, the organic layer obtained is washed with H_2O and brine, dried and solvent is evaporated. 3-O-Benzyloxymethyl-6-deacetyl-Cephalosporin P1 benzyloxymethylester is obtained.

^{1}H-NMR (200MHz, DMSO): δ (ppm) = 7.26-7.32 (m, 10H, arom.-H), 5.68 (d, J=8.2Hz, H-16), 5.32 (dd, J=6.2Hz, J=18.8Hz, 2H, BOM-CH_2), 5.08 (t, 1H, 24-H), 4.47-4.81 (m, 6H, 3x BOM-CH_2), 3.51 (s, 1H, 3-H), 3.49/3.34 (2s, 1H, 6-H, 7-H), 1.85 (1s, 3H, H-34).

^{13}C-NMR (50MHz, DMSO): δ (ppm) = 169.56, 168.57, 149.13, 138.18, 137.10, 131.67, 129.09, 128.21, 128.15, 127.66, 127.50, 127.35, 127.27, 123.0, 92.97, 88.18, 82.84, 78.32, 75.84, 73.75, 71.12, 68.62, 49.05, 47.88, 43.55, 42.48, 36.23, 35.66, 30.02, 28.13, 27.89, 25.96, 25.59, 25.38, 22.86, 22.37, 20.75, 20.37, 18.71, 18.32, 17.43.

C. 3-O-Benzyloxymethyl-6-O-^{i}butyryl-Cephalosporin P1 benzyloxymethylester (compound of formula VIP, wherein R_1 is isopropyl)

1.4 ml of isobutyric acid are added to a solution of 8.68 g 3-O-benzyloxymethyl-6-deacetyl-Cephalosporin P1 benzyloxymethylester and 1.1 g of DMAP in anhydrous CH_2Cl_2 under argon at 0 °C. 2.80 g of EDCI are added to the mixture obtained and the mixture obtained is stirred at rt overnight. The mixture obtained is concentrated and the concentration residue obtained is distributed between EtOAc and H_2O and extracted. The organic layer obtained is washed with H_2O, brine and saturated, aqueous Na_2CO_3-solution, dried and solvent is evaporated. 3-O-Benzyloxymethyl-6-O-isobutyryl-Cephalosporin P1 benzyloxymethylester is obtained. ^{1}H-NMR (200MHz, DMSO): δ (ppm) = 7.26-7.32 (m, 10H, arom.-H), 5.67 (d, J=8.3Hz, H-16), 5.32 (dd, J=6.2Hz, J=16.7Hz, 2H, BOM-CH_2), 5.04-5.10 (m, 2H, OH, 24-H), 4.49-4.82 (m, 8H, OH, 6-H, 3x BOM-CH_2), 3.53 (s, 1H, 3-H), 3.27 (d, 1H, 7-H), 1.84 (1s, 3H, H-34), 1.05 (m, cont. 2 x 3'-CH_3).

^{13}C-NMR (50MHz, DMSO): δ (ppm) = 175.27, 169.61, 168.48, 149.14, 138.10, 137.0, 131.86, 129.25, 128.22, 128.17, 127.67, 127.50, 127.35, 122.97, 92.97, 88.22, 79.90, 77.79, 77.54, 73.71, 71.14, 68.69, 54.76, 47.92, 42.89, 35.83, 35.19, 33.56, 30.93, 28.15, 27.88, 25.82, 25.62, 25.39, 23.21, 22.89, 21.00, 20.32, 18.75, 18.25, 17.43, 17.13, 16.94, 16.57.

D. 6-O-isobutyryl-24, 25-dihydro-Cephalosporin P1 (compound of formula I, wherein R is -COR_1, wherein R_1 is isopropyl)

4.10 g of 3-O-benzyloxymethyl-6-O-isobutyryl-Cephalosporin P1 benzyloxymethylester are hydrogenated at 1 atm in the presence of $Pd(OH)_2$/C in 20ml of a mixture of EtOAc /MeOH = 10 /1 overnight, the mixture obtained is filtered and solvent is evaporated. 6-O-isobutyryl-24, 25-dihydro-Cephalosporin P1 is obtained.

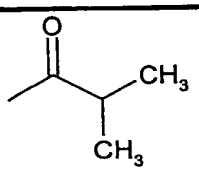
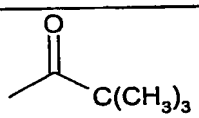
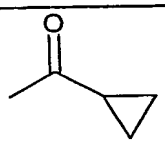
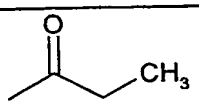
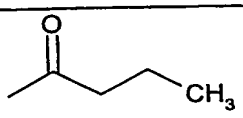
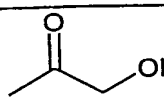
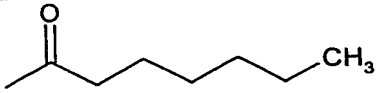
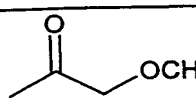
Example 2

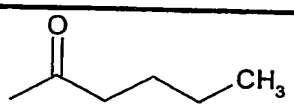
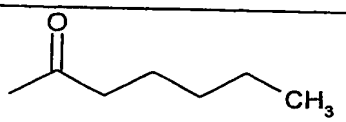
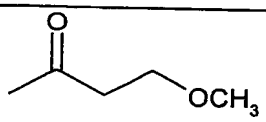
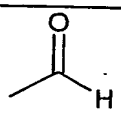
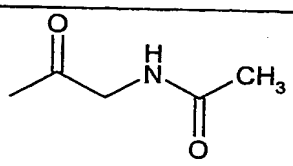
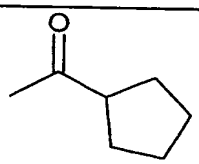
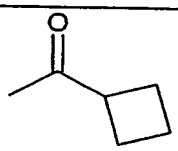
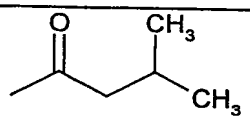
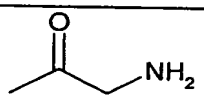
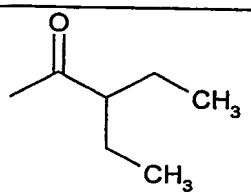
3-O-Benzyloxymethyl-6-O-pivaloyl-Cephalosporin P1 benzyloxymethylester (compound of formula VI_P, wherein R_1 is t.butyl)

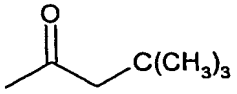
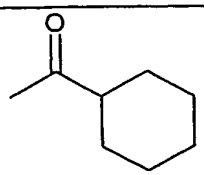
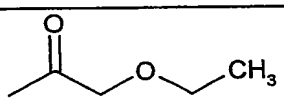
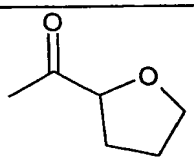
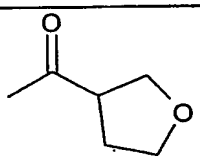
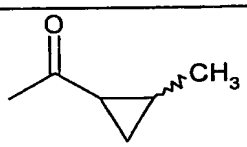
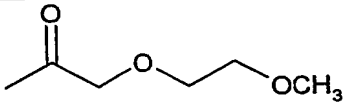
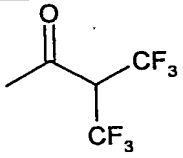
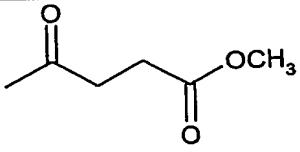
1.31 ml of pivaloyl chloride are added at rt to a solution of 5.504 g of 3-O-benzyloxymethyl-6-deacetyl-Cephalosporin P1 benzyloxymethylester and 1.13 g of DMAP in anhydrous pyridine under argon. The mixture obtained is stirred under argon at 50°C for 20 hours. The mixture obtained is poured over ice and the mixture obtained is extracted with EtOAc. The organic layer obtained is washed with H_2O and brine, dried, and solvent is evaporated. 3-O-Benzyloxymethyl-6-O-pivaloyl-Cephalosporin P1 benzyloxymethylester is obtained. Splitting off the benzoxymethyl protecting group and hydrogenation of the double bond is carried out analogously to Example 1, step D..

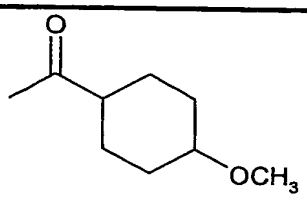
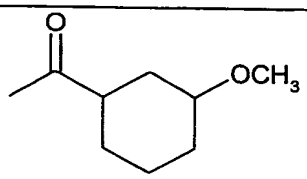
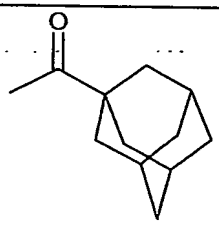
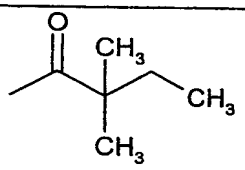
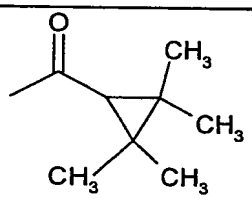
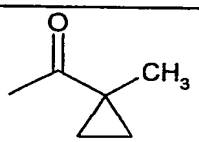
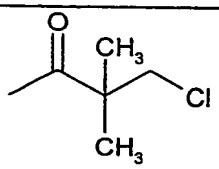
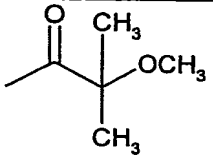
Analogously to the methods as described in examples 1 and 2, but using appropriate starting materials, compounds of formula I, wherein R is as defined in TABLE 1 below, are obtained. ^{1}H-NMR data (in DMSO, if not otherwise indicated) of the compounds are also set out in TABLE 1.

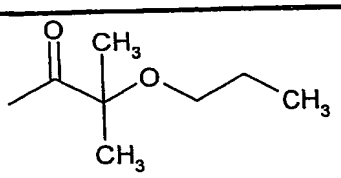
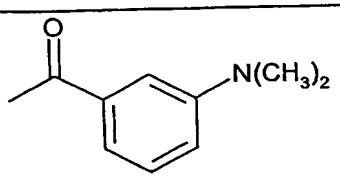
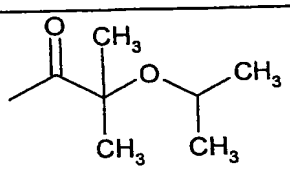
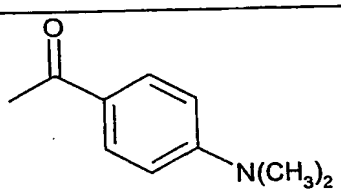
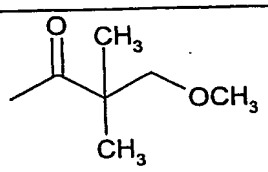
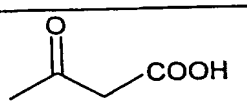
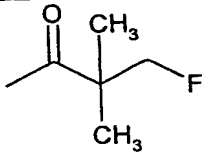
TABLE 1

EX	R	^{1}H-NMR
1		5.82 (d, J=8.7 Hz, 1H, 16-H), 4.53 (d, J=10.6 Hz, 1H, 6-H), 3.71 (d, J=2.1Hz, 1H, 3-H), 3.40 (s, 1H, 7-H), 2.49-2.56 (m, 3H, 13-H, 2'-H, 22a-H), 2.09-2.35 (m, 5H, 22b-H, 5-H, 8-H, 12a-H, 15a-H), 1.94 (s, 3H, 34-CH_3), 1.82-1.89 (m, 3H, 4-H, 2a-H, 11a-H), 1.67-1.72 (m, 3H, 1a-H, 12b-H, 2b-H), 1.35-1.53 (m, 6H, 25-H, 11b-H, 23-CH_2, 15b-H, 1b-H), 1.14-1.19 (m, 14H, 19-CH_3, 2 x 3'-CH_3, 30-CH_3, 24-CH_2), 1.03 (s, 3H, 18-CH_3), 0.89 (d, J=6.9Hz, 3H, 28-CH_3), 8.86 (d, J=6.9Hz, 6H, 26-CH_3, 27-CH_3)
2		5.61 (d, J=8.1Hz, 1H, 16-H), 4.60 (d, J=9.7Hz, 1H, 6-H), 3.47 (s, 1H, 3-H), 3.19 (s, 1H, 7-H), 1.88 (s, 3H, 34-CH_3), 1.13 (s, 9H, 3 x 3'-CH_3)
3		5.62 (d, J=8.2Hz, 1H, 16-H), 4.63 (dd, J=9.7Hz, J=2.0Hz, 1H, 6-H) ,3.47 (s, 1H, 3-H), 3.19 (d, J=2.0Hz, 1H, 7-H), 1.89 (s, 3H, 34-CH_3), 1.21-2.44 (m, 2'-H, 3'-CH_2, 4'-CH_2)
4		5.64 (d, J=7.9Hz, 1H, 16-H), 4.65 (d, J=10.2Hz, 1H, 6-H), 3.48 (s, 1H, 3-H), 3.10 (s, 1H, 7-H), 1.92-2.56 (m, 9H, cont. 2'-CH_2), 1.89 (s, 3H, 34-CH_3), 1.03 (d, J=7.0Hz, 3 H, 3'-CH_3)
5		5.59 (d, J=8.3 Hz, 1H, 16-H), 4.60 (d, J=9.9Hz, 1H, 6-H), 3.47 (s, 1H, 3-H), 3.30 (s, 1H, 7-H), 1.92-2.56 (m, 9H, cont. 2'-CH_2), 1.89 (s, 3H, 34-CH_3), 0.77-1.80 (m, cont. 3'-CH_2, 4'-CH_3)
6		5.57 (d, J=8.3Hz, 1H, 16-H), 4.65 (dd, J=7.9Hz, J=2.5Hz, 1H, 6-H), 3.93 (dd, J=17.1, J=28.5, 2H, 2'-CH_2), 3.45 (s, 1H, 3-H), 3.32 (d, J=2.5Hz, 1H, 7-H)
7		5.60 (d, J=8.2 Hz, 1H, 16-H), 4.60 (d, J=10.0Hz, 1H, 6-H), 3.48 (s, 1H, 3-H), 3.31 (s, 1H, 7-H), 1.92-2.56 (m, 9H, cont. 2'-CH_2), 1.89 (s, 3H, 34-CH_3), 0.76-1.80 (m, cont. 3'-CH_2, 4'-CH_2, 5'-CH_2, 6'-CH_2, 7'-CH_3)
8		5.62 (d, J=6.8Hz, 1H, 16-H), 4.70 (d, J=9.9Hz, 1H, 6-H), 3.84-4.20 (m, 2H, 2'-CH_2), 3.32-3.44 (m, 5H, 3-H, 7-H, -OCH_3)

EX	R	^{1}H-NMR
9		5.62 (d, 1H, 16-H), 4.62 (d, 1H, 6-H), 3.45 (s, 1H, 3-H), 3.33 (s, 1H, 7-H), 1.92-2.56 (m, 9H, cont. 2'-CH_2), 1.88 (s, 3H, 34-CH_3), 0.76-1.80 (m, cont. 3'-CH_2, 4'-CH_2, 5'-CH_3)
10		5.61 (d, 1H, J=8.2Hz, 16-H), 4.61 (d, J=9.3Hz, 1H, 6-H), 3.48 (s, 1H, 3-H), 3.31 (s, 1H, 7-H), 1.92-2.56 (m, 9H, cont. 2'-CH_2), 1.87 (s, 3H, 34-CH_3), 0.76-1.80 (m, cont. 3'-CH_2, 4'-CH_2, 5'-CH_2, 6'-CH_3)
11		5.61 (d, J=8.3Hz, 1H, 16-H), 4.63 (d, J=10.1Hz, 1H, 6-H), 3.53-3.59 (m, 2H, 2'-CH_2), 3.47 (s, 1H, 3-H), 3.32 (s, 1H, 7-H), 3.22 (s, 3H, -OCH_3)
12		8.21 (s, 1H, 1'-H), 5.62 (d, J=7.9Hz, 1H, 16-H), 4.66 (dd, 1H, 6-H), 3.48 (s, 1H, 3-H), 3.38 (d, J=2.8Hz, 1H, 7-H), 1.89 (s, 3H, 34-CH_3)
13		8.28 (dd, J=5.8Hz, 1H, NH), 5.60 (d, J=8.1Hz, 1H, 16-H), 4.64 (dd, J=8.3Hz, J=2.4Hz, 1H, 6-H), 3.60 (dd, J=5.8Hz, 2'-CH_2), 3.47 (s, 1H, 3-H), 3.34 (d, J=2.4Hz, 1H, 7-H), 1.85/1.87 (2s, 2x3H, 34-CH_3, 4'-CH_3)
14		5.61 (d, J=7.7Hz, 1H, 16-H), 4.60 (d, J=9.8Hz, 1H, 6-H) ,3.47 (s, 1H, 3-H), 3.25 (s, 1H, 7-H), 2.48-2.84 (m, 2'-H), 1.88 (s, 3H, 34-CH_3), 1.00-2.45 (m, 3'-CH_2, 4'-CH_2, 5'-CH_2, 6'-CH_2)
15		5.61 (d, J=8.3Hz, 1H, 16-H), 4.61 (d, J=10.0Hz, 1H, 6-H) ,3.46 (s, 1H, 3-H), 3.27 (s, 1H, 7-H), 3.09 (quin, J=8.3Hz, 2'-H)
16		5.64 (d, J=8.33Hz, 1H, 16-H), 4.63 (d, J=10.0Hz, 1H, 6-H), 3.48 (s, 1H, 3-H), 3.35 (s, 1H, 7-H), 1.95-2.50 (m, cont. 2'-CH_2, 3'-H), 1.90 (s, 3H, 34-CH_3), 0.96/0.95/0.93/0.92 (4s, 4x4'-CH_3).
17		5.61 (d, J=8.3Hz, 1H, 16-H), 4.67 (d, 1H, 6-H), 3.47 (s, 1H, 3-H), 3.09-3.40 (m, 5H, 7-H, 2'-CH_2, NH_2)
18		5.60 (d, J=8.5Hz, 1H, 16-H), 4.60 (d, J=10.0Hz, 1H, 6-H), 3.49 (s, 1H, 3-H), 3.32 (s, 1H, 7-H), 1.87 (s, 3H, 34-CH_3), 1.12/1.00 (2s, 2x3H, 4'-CH_3)

EX	R	^{1}H-NMR
19		5.61 (d, J=7.9Hz, 1H, 16-H), 4.60 (d, J=10.3Hz, 1H, 6-H), 3.49 (s, 1H, 3-H), 3.35 (s, 1H, 7-H), 1.89 (s, 3H, 34-CH_3), 1.00 (s, 9H, 4'-CH_3)
20		5.63 (d, J=8.3Hz, 1H, 16-H), 4.59 (d, J=9.9Hz, 1H, 6-H), 3.47 (s, 1H, 3-H), 3.24 (s, 1H, 7-H), 0.99-2.35 (m, cont. 2'-H, 3'-CH_2, 4'-CH_2, 5'-CH_2, 6'-CH_2, 7'-CH_2)
21		5.64 (d, J=8.3Hz, 1H, 16-H), 4.72 (d, J=8.8Hz, 1H, 6-H), 3.90-4.18 (m, 2H, 2'-CH_2), 3.36-3.57 (m, 4H, 3-H, 7-H, 4'-CH_2)
22		5.61 (m, 1H, 16-H), 4.6-4.7 (m, 1H, 6-H), 4.19-4,35 (m, 1H, H-2'), 3.80 (m, 2H, 4'-CH_2), 3.34-3.45 (m, 2H, 3-H, 7-H)
23		5.62 (d, J=7.5Hz, 1H, 16-H), 4.65 (d, J=9.5Hz, 6-H), 3.03-3.93 (m, 3'-CH_2, 5'-CH_2, 3-H, 7-H)
24		5.61 (d, J=8.3Hz, 1H, 16-H), 4.60 (d, J=11.2Hz, 6-H), 3.47 (s, 1H, 3-H), 3.28 (s, 1H, 7-H), 1.04 (s, 3H, -CH_3(3'-C))
25		5.64 (d, J=8.3Hz, 1H, 16-H), 4.72 (d, J=8.9Hz, 1H, 6-H), 4.09 (dd, 2H, 2'-CH_2), 3.60-3.64/3.46-3.50 (2m, 5H, 4'-CH_2, 5'-CH_2, 3-H), 3.37 (s, 1H, 7-H), 3.27 (s, 3H, -OCH_3)
26		5.84 (d, J=8.7Hz, 1H, 16-H), 4.77 (d, J=10.5Hz, 6-H), 4.10 (sept., 1H, 2'-H), 3.74 (s, 1H, 3-H), 3.50 (s, 1H, 7-H)
27		5.58 (d, J=8.3Hz, 1H, 16-H), 4.57 (d, J=10.1Hz, 6-H), 3.57 (s, 3H, -OCH_3), 3.45 (s, 1H, 3-H), 3.29 (s, 1H, 7-H).

EX	R	^{1}H-NMR
28		5.61 (d, J=8.1Hz, 1H, 16-H), 4.60 (d, J=9.8Hz, 1H, 6-H), 3.10-3.48 (m, 6H, 5'-H, OCH_3, 3-H, 7-H)
29		5.61 (d, J=8.0Hz, 1H, 16-H), 4.61 (d, J=10.0Hz, 1H, 6-H), 3.49 (s, 1H, 3-H), 3.05-3.30 (m, 5H, 4'-H, OCH_3, 7-H)
30		5.62 (d, J=8.2Hz, 1H, 16-H), 4.59 (d, J=9.7Hz, 1H, 6-H), 3.45 (s, 1H, 3-H), 3.17 (d, 1H, 7-H), 1.40-2.45 (m, cont. adamantyl – CH and CH_2)
31		5.63 (d, 1H, 16-H), 4.60 (d, J=10.1Hz, 1H, 6-H), 3.46 (s, 1H, 3-H), 3.26 (s, 1H, 7-H), 1.87 (s, 3H, 34-CH_3), 1.00-1.24 (m, cont. 12H, 2 x CH_3 (C-2'), 4'-CH_3)
32		5.63 (d, J=8.2Hz, 1H, 16-H), 4.56 (d, J=10.2Hz, 6-H), 3.45 (s, 1H, 3-H), 3.29 (s, 1H, 7-H), 1.15 (s, 12H, 4 x -CH_3(3'-C))
33		5.63 (d, J=8.2Hz, 1H, 16-H), 4.60 (d, J=10.0Hz, 6-H), 3.45 (s, 1H, 3-H), 3.24 (s, 1H, 7-H), 0.70-1.80 (m, 39H, cont. -CH_3(2'-C), 3'-CH_2, 4'-CH_2)
34		5.62 (d, J=8.2Hz, 1H, 16-H), 4.63 (d, J=9.8Hz, 1H, 6-H), 3.73 (dd, J=10.7Hz, J=15.9Hz, 2H, -CH_2Cl), 3.47 (s, 1H, 3-H), 3.35 (d, 1H, 7-H), 1.87 (s, 3H, 34-CH_3), 1.20 (s, 6H, 2 x CH_3 (C-2')
35		5.63 (d, J=8.4Hz, 1H, 16-H), 4.66 (d, J=10.0Hz, 1H, 6-H), 3.46 (s, 1H, 3-H), 3.26 (d, 1H, 7-H), 3.16 (s, 3H, OCH_3), 1.87 (s, 3H, 34-CH_3), 1.31 (s, 6H, 2 x CH_3 (C-2')

EX	R	^{1}H-NMR
36		5.62 (d, J=8.1Hz, 1H, 16-H), 4.65 (d, J=9.9Hz, 1H, 6-H), 3.17-3.55 (m, 4H, 3-H, 7-H, -OCH_2), 1.87 (s, 3H, 34-CH_3), 1.32 (s, 6H, 2 x CH_3 (C-2')
37		7.28-7.38 (m, 3H, arom.H), 6.93 (d, 1H, arom.H), 5.76 (d, J=8.6Hz, 1H, 16-H), 4.79 (d, J=11.2Hz, 1H, 6-H), 3.70 (s, 1H, 3-H), 3.61 (d, 1H, 7-H), 2.98 (s, 6H, -$N(CH_3)_2$)
38		5.77 (d, J=8.4Hz, 1H, 16-H), 4.51 (d, J=10.5Hz, 1H, 6-H), 3.60-3.74 (m, 2H, 3-H, -OC<u>H</u>$(CH_3)_2$), 3.34 (s, 1H, 7-H), 1.88 (s, 3H, 34-CH_3), 1.00-1.50 (m, cont., 2 x CH_3 (C-2'), -OCH($C\underline{H_3}$)$_2$)
39		7.82 (d, J=8.9Hz, 2H, arom.H), 6.57 (d, J=8.9Hz, 2H, arom.H), 5.71 (d, J=8.4Hz, 1H, 16-H), 4.67 (d, J=10.5Hz, 1H, 6-H), 3.63 (s, 1H, 3-H), 3.52 (d, 1H, 7-H), 2.96 (s, 6H, -$N(CH_3)_2$)
40		5.81 (d, J=8.3Hz, 1H, 16-H), 4.62 (d, J=10.4Hz, 1H, 6-H), 3.69 (s, 1H, 3-H), 3.25-3.45 (m, 5H, 7-H, -OCH_3), 1.92 (s, 3H, 34-CH_3), 1.16 (s, 6H, 2 x CH_3 (C-2')
41		5.86 (d, 1H, 16-H), 4.74 (d, J=9.1Hz, 1H, 6-H), 3.32-3.79 (m, 4H, 3-H, 7-H, 2'-CH_2)
42		5.82 (d, J=8.4Hz, 1H, 16-H), 4.58 (d, J=10.8Hz, 1H, 6-H), 4.50/4.26 (ddd, J=8.8Hz, H=13.2Hz, J=47.1Hz, 2H, -CH_2F), 3.70 (s, 1H, 3-H), 3.38 (s, 1H, 7-H), 1.93 (s, 3H, 34-CH_3), 1.15-1.21 (m, cont.6H, 2 x CH_3 (C-2')

The compounds of examples 2, 30, 31 and 34 in TABLE 1 are obtained analogously as described on Example 2, but using appropriate starting materials; all other compounds of TABLE 1 are obtained analogously as described in Example 1, but using appropriate starting materials.

Example 43

6-O-Methyl-24, 25-dihydro-Cephalosporin P1 (compound of formula I_P, wherein R is methyl)

A. 3-O-Benzyloxymethyl-6-O-methyl-24, 25-dihydro-Cephalosporin P1 diphenylemthylester

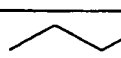
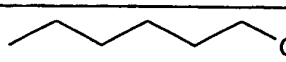
0.67 ml of LiHMDS (1M in THF) are added to a solution of 500 mg of 3-O-Benzyloxymethyl-6-deacetyl-Cephalosporin P1 diphenylmethylester in 5 ml of dry N,N-dimethylformamide at -10° and to the mixture obtained 0.06 ml of methyliodide is added after 10 minutes. The mixture obtained is stirred at room temperature for 2 hours. The mixture obtained is poured onto ice and the mixture obtained is extracted three times with EtOAc. The organic layer obtained is dried, solvent is evaporated and the evaporation residue obtained is subjected to chromatography. 3-O-Benzyloxymethyl-6-O-methyl-Cephalosporin P1 diphenylmethylester is obtained.

B. 6-O-Methyl-24, 25-dihydro-Cephalosporin P1

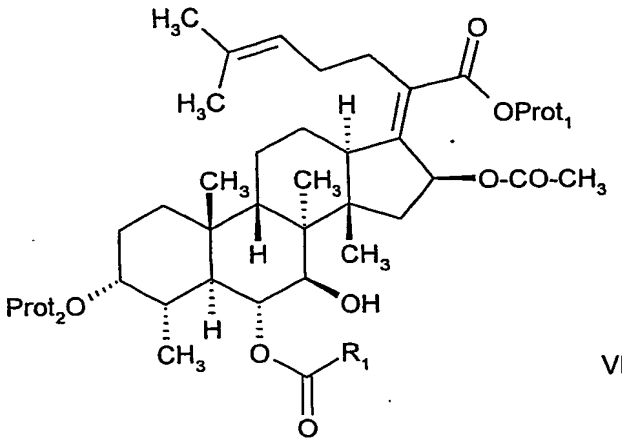
241 mg of 3-O-benzyloxymethyl-6-O-methyl-Cephalosporin P1 diphenylmethylester are hydrogenated at 1 atm in the presence of $Pd(OH)_2/C$ in 3ml of EtOAc overnight, the mixture obtained is filtered, solvent is evaporated and the evaporation residue is subjected to chromatography. 6-O-methyl-24, 25-dihydro-Cephalosporin P1 is obtained.

Analogously as described in Example 43, but using appropriate starting materials, compounds of formula I, wherein R is as defined in TABLE 2 below, are obtained. ^{1}H-NMR data (in DMSO, if not otherwise indicated) of the compounds are also set out in TABLE 2.

TABLE 2

EX	R	^{1}H-NMR
43		5.65 (d, J=8.3Hz, 1H, 16-H), 3.34-3.53 (m, 2H, 3-H, 7-H), 3.19 (s, 3H, -OCH_3), 2.80 (d, 1H, J=9.6Hz, 6-H)
44		5.66 (d, 1H, 16-H), 3.21-3.65 (m, 4H, -OCH_2, 3-H, 7-H), 2.91 (d, 1H, 6-H)
45		5.64 (d, J=8.3Hz, 1H, 16-H), 3.14-3.53 (m, 4H, -OCH_2, 3-H, 7-H), 2.88 (d, J=9.5Hz, 1H, 6-H)
46		5.54 (d, J=8.4Hz, 1H, 16-H), 3.08-3.40 (m, 4H, -OCH_2, 3-H, 7-H), 2.76 (d, J=9.2Hz, 1H, 6-H)

In TABLE 3 below there are listed mass spectroscopy data of intermediates of formula



VII_P

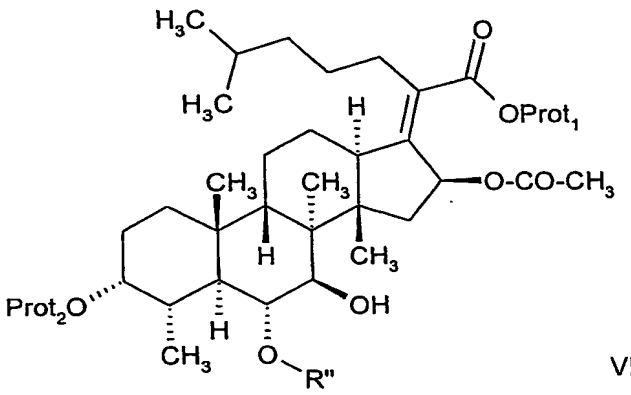
wherein R_1 is as defined in TABLE 3, useful in the production of a compound of formula I_P. The numbers in column "EX", marked with an apostroph (e.g. 1'), are intermediates used in the production of a the corresponding compound of formula I_P in TABLE 1. E.g. the intermediate "1'" in TABLE 3 is the intermediate used in the production of the compound of Example 1 in TABLE 1. Mass spectroscopy data (m/z (ESI)), also set out in TABLE 3, are determined by a Finnigan Navigator ThermoQuest LC/MS system.

TABLE 3

EX	$Prot_2$	R_1	$Prot_1$	m/z (ESI)
1'	BOM	isopropyl	BOM	$[M+Na]^+$ = 865.5
2'	BOM	t.butyl	BOM	$[M+Na]^+$ = 879.5
3'	BOM	cyclopropyl	DPM	$[M+Na]^+$ = 909.4
4'	H	ethyl	DPM	$[M+Na]^+$ = 777.3
5'	H	n-propyl	DPM	$[M+Cl]^-$ = 803.4
6'	BOM	benzyloxymethyl	DPM	$[M]^+$ = 989.4
7'	BOM	n-hexyl	DPM	$[M+Na]^+$ = 953.5
8'	BOM	methoxymethyl	DPM	$[M+Na]^+$ = 914.1
9'	BOM	n-butyl	DPM	$[M+Na]^+$ = 925.0
10'	BOM	n-pentyl	DPM	$[M+Na]^+$ = 939.2
11'	BOM	methoxyethyl	DPM	$[M+Na]^+$ = 926.9
12'	BOM	hydrogen	DPM	$[M+Na]^+$ = 869.0
13'	BOM	methylcarbonylaminomethyl	DPM	$[M+Cl]^-$ = 951.9
14'	BOM	cyclopentyl	DPM	$[M+Na]^+$ = 937.0
15'	BOM	cyclobutyl	DPM	$[M+Na]^+$ = 923.0

EX	$Prot_2$	R_1	$Prot_1$	m/z (ESI)
16'	BOM	isobutyl	DPM	$[M+Na]^+$ = 925.0
17'	BOM	N-benzyloxycarbonyl-aminomethyl	DPM	$[M+Na]^+$ = 1031.8
18'	BOM	2-ethyl-propyl	DPM	$[M+Na]^+$ = 938.8
19'	BOM	t-butyl-methyl	DPM	$[M+Na]^+$ = 939.0
20'	BOM	cyclohexyl	DPM	$[M+Na]^+$ = 951.0
21'	BOM	ethoxymethyl	DPM	$[M+Na]^+$ = 927.1
22'	BOM	tetrahydrofuran-2-yl	DPM	$[M+Na]^+$ = 939.3
23'	BOM	tetrahydrofuran-3-yl	DPM	$[M+Na]^+$ = 939.3
24'	BOM	2-methyl-cyclopropyl	DPM	$[M+Na]^+$ = 923.2
25'	BOM	methoxy-ethoxy-methyl	BOM	$[M+Na]^+$ = 911.5
26'	BOM	di-trifluoromethyl-methyl	BOM	$[M]^+$ = 950.4
27'	BOM	methoxycarbonylethyl	BOM	$[M+Na]^+$ = 909.2
28'	BOM	4-methoxy-cyclohexyl	BOM	$[M+Na]^+$ = 935.5
29'	BOM	3-methoxy-cyclohexyl	BOM	$[M+Na]^+$ = 935.5
30'	BOM	adamantan-1-yl	BOM	$[M+Na]^+$ = 957.6
31'	BOM	1,1-dimethyl-propyl	BOM	$[M+Na]^+$ = 894.0
32'	BOM	2,2,3,3-tetramethyl-cyclopropyl	BOM	$[M+Na]^+$ = 919.0
33'	BOM	1-methyl-cyclopropyl	BOM	$[M+Na]^+$ = 877.4
34'	BOM	1,1-dimethyl-2-chloro-ethyl	BOM	$[M+Na]^+$ = 913.4
35'	BOM	(methoxy)(dimethyl)methyl	BOM	$[M+Na]^+$ = 895.4
36'	BOM	(n-propoxy)(dimethyl)methyl	BOM	$[M+Na]^+$ = 921.6
37'	BOM	3-dimethylamino-phenyl	BOM	$[M+Na]^+$ = 942.5
38'	BOM	(iso-propoxy)(dimethyl)methyl	BOM	$[M+Na]^+$ = 923.7
39'	BOM	4-dimethylamino-phenyl	BOM	$[M+Na]^+$ = 942.5
40'	BOM	1,1-dimethyl-2-methoxy-ethyl	BOM	$[M+Na]^+$ = 909.5
41'	BOM	benzyloxycarbonyl-methyl	BOM	$[M+Na]^+$ = 972.2
42'	BOM	1,1-dimethyl-2-fluoro-ethyl	BOM	$[M+Na]^+$ = 897.8

In TABLE 4 below there are listed mass spectroscopy data of intermediates of formula



$VIII_P$

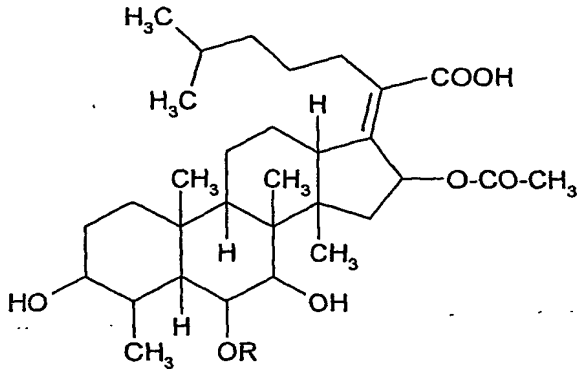
wherein R" is as defined in TABLE 4, useful in the production of a compound of formula I_P. The numbers in column "EX", marked with an apostroph (e.g. 43'), are intermediates used in the production of a the corresponding compound of formula I_P in TABLE 2. E.g. the intermediate "43'" in TABLE 4 is the intermediate used in the production of the compound of Example 43 in TABLE 2. Mass spectroscopy data (m/z (ESI)), also set out in TABLE 4, are determined by a Finnigan Navigator ThermoQuest LC/MS system.

TABLE 4

EX	$Prot_2$	R"	$Prot_1$	m/z (ESI)
43'	BOM	methyl	DPM	$[M+Na]^+$ = 855.1
44'	BOM	ethyl	DPM	$[M+Na]^+$ = 869.4
45'	BOM	n-propyl	DPM	$[M+Na]^+$ = 883.3
46'	BOM	n-hexyl	DPM	$[M+Na]^+$ = 925.5

Patent Claims

1. A compound of formula



I

wherein

R is hydrogen, CO-R_1 or (C_{1-8})alkyl, such as methyl, ethyl, n-propyl or n-hexyl, and

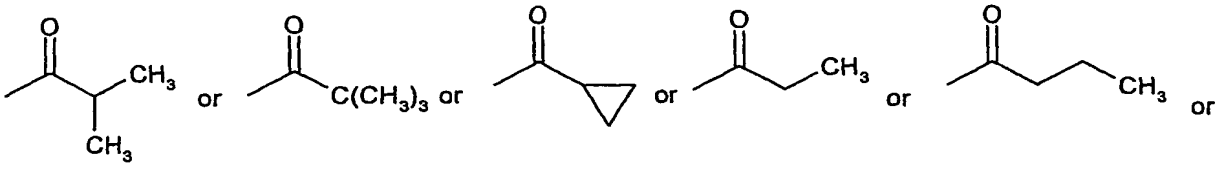
R_1 is hydrogen, (C_{1-8})alkyl, (C_{3-8})cycloalkyl, (C_{1-8})alkoxy-(C_{1-6})alkyl, (C_{1-4})alkoxy-(C_{1-4})alkoxy-(C_{1-4})alkyl, amino(C_{1-4})alkyl, halo(C_{1-6})alkyl, hydroxy(C_{1-4})alkyl, carboxy(C_{1-4})alkyl, (C_{1-4})alkoxycarbonyl-(C_{1-4})alkyl, (C_{6-18})aryl, heterocyclyl having 5 or 6 ring members and 1 to 4 heteroatoms selected from S, O or N, or brigded (C_{7-12})cycloalkyl.

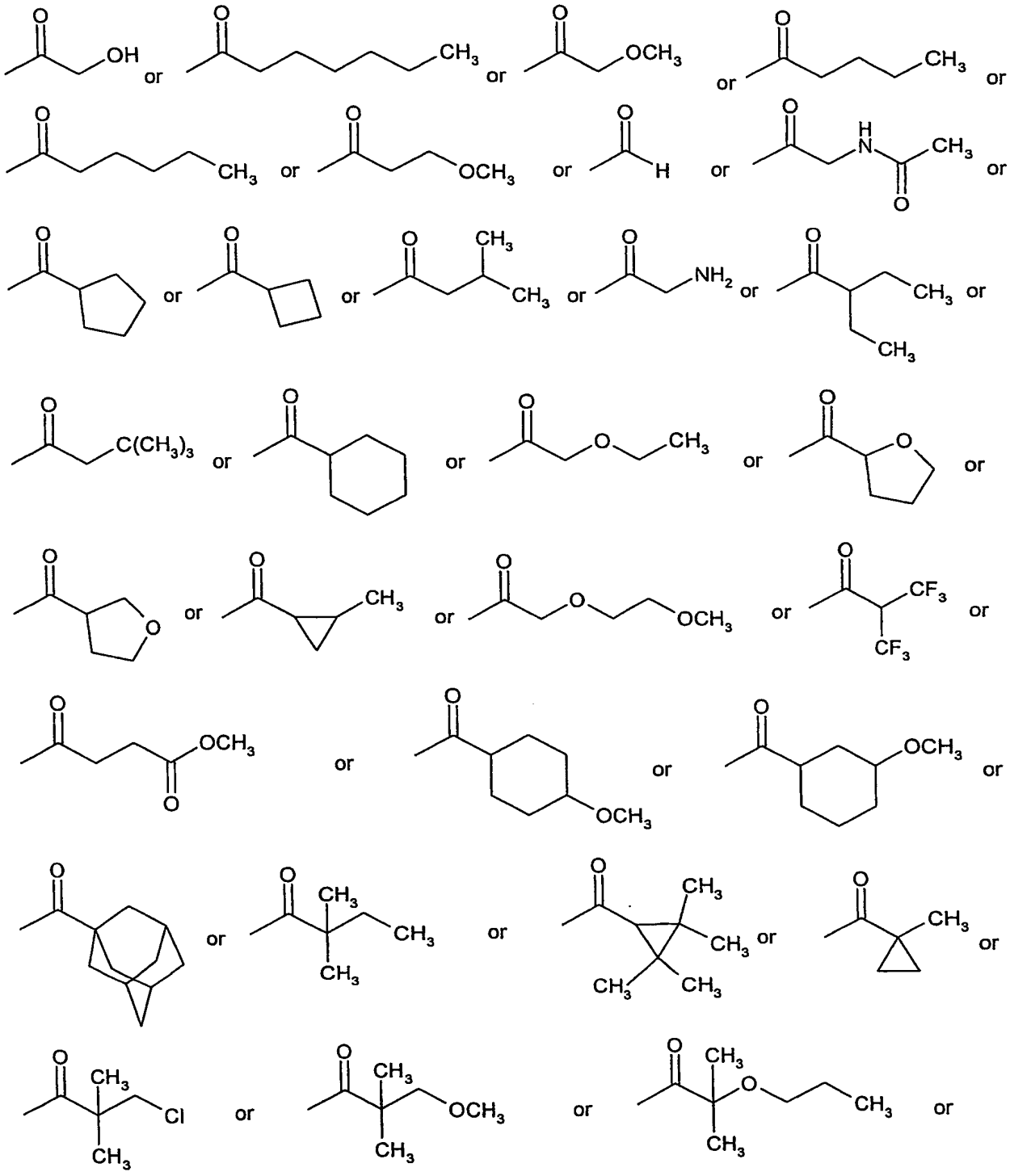
2. A compound of claim 1, wherein

R is hydrogen, (C_{1-6})alkyl, or CO-R_1, and

R_1 is hydrogen, (C_{1-6})alkyl, (C_{3-6})cycloalkyl, e.g. unsubstituted (C_{3-6})cycloalkyl or (C_{3-6})cycloalkyl substituted by one or more methyl or methoxy; (C_{1-3})alkoxy-(C_{1-3})alkyl, methoxy-(C_{1-2})alkoxy-(C_{1-2})alkyl, aminomethyl, halo(C_{1-4})alkyl, comprising one or two halogen atoms; hydroxymethyl, carboxymethyl, methoxycarbonyl-(C_{1-2})alkyl, phenyl, tetrahydrofuranyl or adamantanyl.

3. A compound of any one of claims 1 or 2, wherein R is a group of formula




OH
or
CH3
or
OCH3
or
CH3
or
CH3
or
OCH3
or
H
or
H
N
CH3
O
or
or
CH3
or
NH2
or
CH3
CH3
or
C(CH3)3
or
O
CH3
or
O
or
or
O
CH3
or
O
OCH3
or
CF3
CF3
or
OCH3
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CH3
CH3
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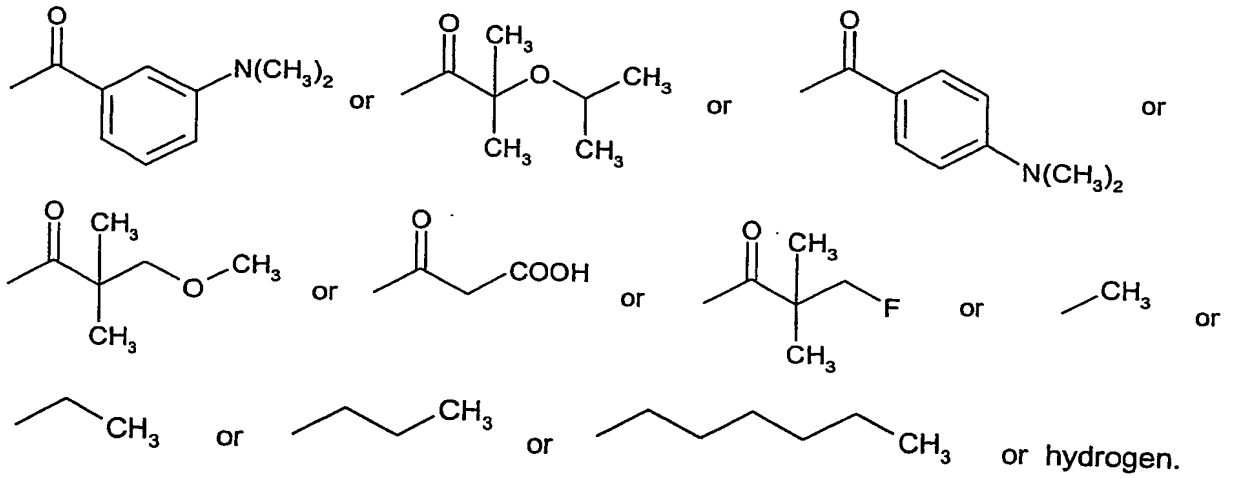


4. A compound of any one of claims 1 or 3 in the form of a salt.

5. A compound of any one of claims 1 to 4 for use as a pharmaceutical.

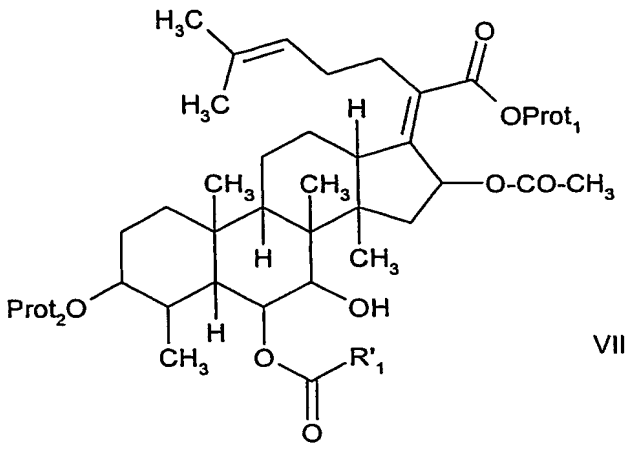
6. The use of a compound of any one of claims 1 to 4 for the manufacture of a medicament for the treatment of microbial diseases.

7. A pharmaceutical composition comprising a compound of any one of claims 1 to 4 in association with at least one pharmaceutical excipient.

8. A pharmaceutical composition according to claim 7, further comprising another pharmaceutically active agent.

9. A method of treatment of microbial diseases, which treatment comprises administering to a subject in need of such treatment an effective amount of a compound of any one of claims 1 to 4.

10. A compound of formula



VII

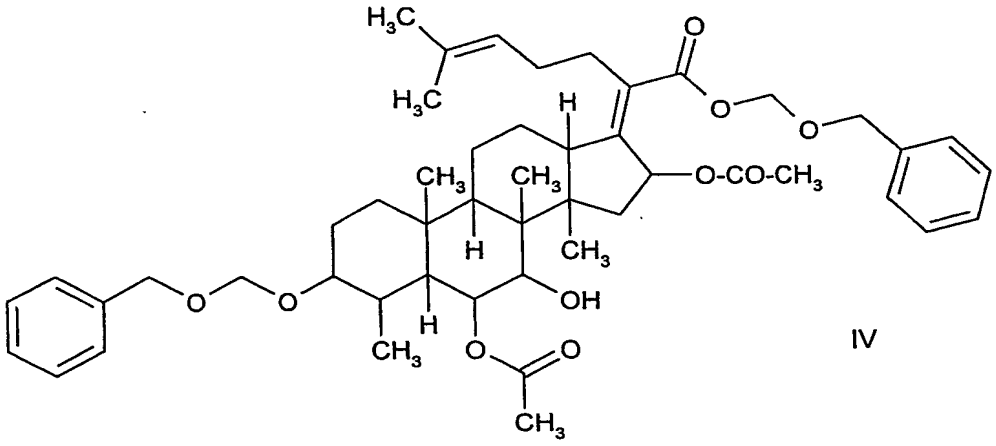
wherein

$Prot_1$ is a protecting group, and

$Prot_2$ is either other than a protecting group, or is a protecting group, and

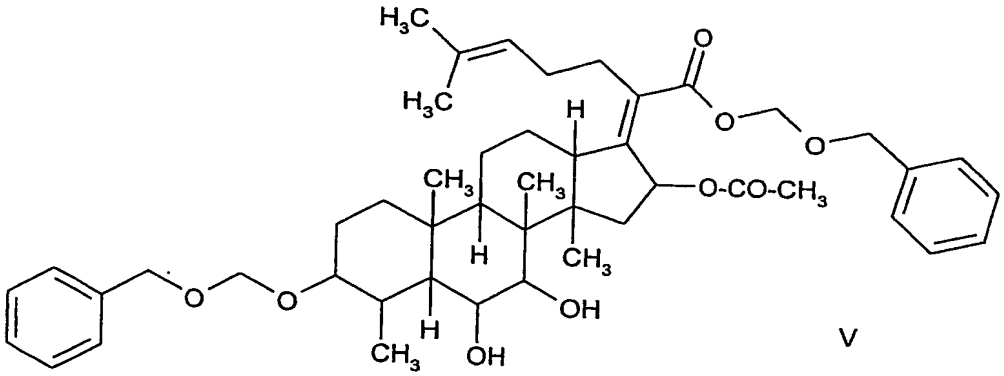
R'_1 has the meaning of R_1, as defined in any one of claims 1 to 4, and additionally includes residues as defined in R_1, wherein functional groups are protected.

11. A compound of formula



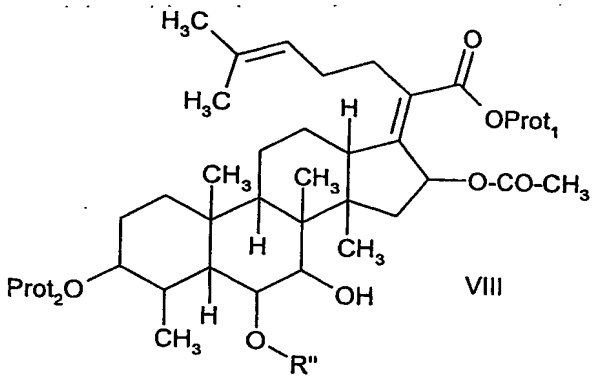
IV

or of formula



V

12. A compound of formula



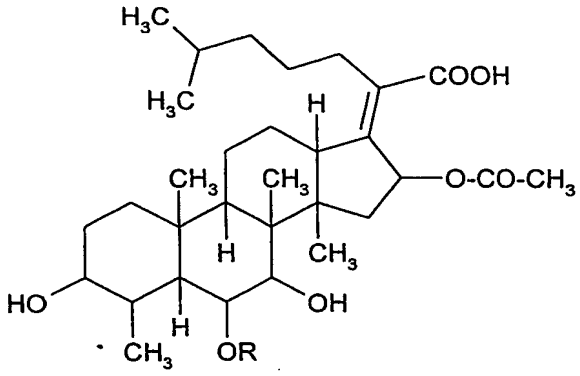
VIII

wherein $Prot_1$ and $Prot_2$ are as defined in claim 10, and R" is (C_{1-8})alkyl.

SC/3-Nov-03

Abstract

A compound of formula



I

wherein

R has various meanings and its use as a pharmaceutical.